DAMAGE CONTROL RESUSCITATION AT LEVEL IIb/III TREATMENT FACILITIES

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Reviewed:	Jan 2009	Approved:	13 Feb 09	
Supersedes:	Damage Control Resuscitation at Level IIb / III Treatment Facilities, updated 26 Nov 2008			
☒ Minor Changes (***or***)	☐ ***Changes are substantial and require a thorough reading of this CPG*** (***or***)			
☐ Significant Changes	Defines 1 unit/pack apheresis platelets = 6 units donor platelets; emphasizes the use of Fresh Whole Blood for massive transfusion when full component therapy is not available or is not adequately resuscitating the casualty; updated supporting documentation and references.			

1. Goal. Outline a method of trauma resuscitation in which fluids, blood products and other adjunctive measures, e.g. Recombinant Factor VIIa (rFVIIa) are used to reverse or prevent coagulopathy and aid in management of ongoing hemorrhage.

2. Background.

a. Utilizing the Tactical Combat Casualty Care (TCCC) guidelines, medics and corpsmen use tourniquets and hemostatic dressings to treat most compressible hemorrhage on the battlefield. Non-compressible hemorrhage (i.e., truncal, axillary, neck, and groin) remains a largely unsolved problem, as well as one of the leading causes of death on today's battlefield.

b. Following Advanced Trauma Life Support guidelines, physicians have traditionally initiated resuscitation with large-volume crystalloid infusion, followed by the addition of pRBCs and finally plasma. This approach in major civilian trauma has demonstrated a greater incidence of abdominal compartment syndrome (16% vs. 8%), multiple organ failure (22% vs. 9%), and death (27% vs. 11%).

c. There is strong retrospective evidence in both civilian and military trauma populations, that for patients requiring massive transfusion, a higher proportion of plasma and platelets, when compared to red cells, results in improved survival (e.g. 1 unit plasma: 1 unit platelets: 1 unit of PRBs). Fresh whole blood delivers these products in the above ratio and is independently associated with improved survival in a retrospective analysis. Finally, there is retrospective evidence that rFVIIa used early in the resuscitation of patients with massive transfusion results in decreased blood usage and improved survival.

3. Recognition of patients requiring damage control resuscitation.

a. Most casualties that receive hemostatic resuscitation in the ED or the OR require a massive transfusion (MT). Defined as equal to as, or greater than, 10u pRBCs/24 hours, MT patients present a unique challenge both in the ED and OR, as well as the ICU post-operatively. Anticipating the need for a MT requires experience and the coordination of extensive resources.

b. A number of risk factors for massive transfusion upon hospital admission have been identified (13). In a patient with **serious injuries**, these include:

1) Systolic blood pressure < 110 mm Hg
2) Heart rate > 105 bpm
3) Hematocrit < 32%
4) pH < 7.25

Note: Patients with 3 of the above 4 risk factors have approximately a 70% risk of massive transfusion; patients with all 4 of the above have an 85% risk.

5) Other risk factors for massive transfusion include: INR level > 1.4 (15), NIR-derived StO2< 75% (14).

c. Examples of clinical scenarios that increase risk of need for massive transfusion include: Uncontrolled truncal, axillary, neck, or groin bleeding, uncontrolled bleeding secondary to large soft tissue injuries, proximal amputation or mangled extremity, clinical signs of coagulopathy, or severe hypothermia associated with blood loss.

4. Management Principles for Damage Control Resuscitation

a. The major principle of damage control resuscitation is to prevent development of coagulopathy by dilution of factors needed to provide hemostasis. In order to support this goal, the system must provide components at an appropriate ratio throughout the resuscitation process.

b. It is key to communicate with the Bloodbank at the medical treatment facility when a potential massive transfusion patient has been identified. Most blood banks within theater have developed protocols for providing blood products in the appropriate proportion to support resuscitative efforts.

c. Component therapy: The goal in transfusion of the patient with need for massive transfusion is to deliver a ratio of PRBCs to plasma to platelets of 1:1:1

Note: All platelets at US Level III facilities are apheresis platelets.
1 apheresis unit/pack = 6 units random donor platelets.

Therefore, the goal of 1:1:1 resuscitation should be 6 units pRBCs : 6 units FFP : 1 unit/pack apheresis platelets). This goal should be discussed at appropriate intervals between members of the trauma team and blood bank and efforts made to develop a massive transfusion protocol (see Appendix A).

1) Packed red blood cells (PRBCs): There is evidence that as PRBCs are stored, that **there is development of a "storage lesion" that may have deleterious effects**. These effects are potentially more significant in patients requiring MT. For MT patients the policy of "Last in/First Out" (LIFO) will be applied for all PRBCs provided to the surgical/ICU team. The CENTCOM Blood Bank staff, in conjunction with in-theater personnel and the USAF, has developed an extensive logistical process that helps ensure that major Level III facilities within the theater are adequately supported with the newest and freshest pRBCs (see appendix B). Frozen and deglycerolized RBCs are available at several facilities within the CENTCOM AOR. Use of these products is somewhat limited due to the time necessary for

preparation (90 min-2 hours). Current experience with this product in the setting of massive transfusion is limited, therefore, this product should not be utilized in this setting unless other blood supplies are limited. Further information on this product is available in the CENTCOM JTTS CPG entitled "Frozen and Deglycerolized Red Blood Cells, Nov 2008".

2) Thawed plasma for emergency use should be type A or AB. An effort should be made to rapidly obtain the casualty's blood type, with the goal to provide type-specific transfusions as quickly as possible during the resuscitation process.

3) Platelets: Apheresis platelets collected in theater are non-FDA approved due to the lack of complete infectious disease testing of donors prior to collection. Efforts have been made to push platelets as a component of therapy to Level III facilities throughout the two theaters. These are typically available as platelet pheresis packs with these obtained from donors within theater.

4) Cryoprecipitate may be added to component therapy depending on the judgment of the care provider.

5) Warm fresh whole blood (FWB): FWB offers an appropriate ratio of components, with the benefits of lack of storage lesion, excellent platelet activity, and field availability. While broadly available and used, this treatment option is not FDA-approved due to a slight risk of transmission of infection. Recent retrospective data show a potential survival benefit to the use of FWB during resuscitation of severe combat injuries. Fresh whole blood can be used at any phase of the resuscitation if it is the judgment of the provider that the casualty has a life-threatening hemorrhagic injury and one of the blood components (platelets, plasma, RBCs) is not available OR when stored components are not adequately resuscitating a patient receiving component therapy (e.g. worsening coagulopathy and shock). For additional information, see CENTCOM JTTS CPG entitled "Fresh Whole Blood (FWB) Transfusion, Jan 2009.

d. Recombinant Factor VIIa **(rFVIIa)** has recently been associated with improved hemostasis in combat casualties, decreasing blood loss by 23% (see Appendix C for more information on the use of rFVII**a**). The use of this product should be reserved for those patients likely to require massive transfusion (e.g. significant injury and 3 or 4 risk factors) and is at the discretion of the treating physician. It should be the judgement of the provider that the casualty has a life-threatening hemorrhagic injury and high potential for development of coagulopathy or presence of coagulopathy.

1) Usual Dose: 100 mcg/kg intravenously; May be repeated in 20 minutes

2) Contraindications: Active cardiac disease

3) Storage: Refrigerate (2°C – 8°C/36°F – 46°F) prior to reconstitution and use. The FDA recently approved a room temperature stable product. This will be distributed throughout the CENTCOM AOR as the current supplies are exhausted.

5. Emergency Department (ED) Resuscitation. Damage control resuscitation (pRBC, plasma and platelets (1:1:1 ratio) $\pm$ rFVIIa) should be initiated for patients with signs noted in

section 3 above. Transfusion of products and administration of rFVIIa should be based on clinician judgement and the response of the patient to resuscitative therapy. Crystalloid and nonsanguinous colloid therapy should be limited in the patient with significant ongoing bleeding.

6. OR Resuscitation.

a. The goal of resuscitation in the OR is to stop bleeding, to normalize casualty temperature, and to prevent/reverse coagulopathy and shock. In addition to ongoing resuscitation with component therapy the following measures are suggested:

1) The operating room must be kept as warm as possible; ideally 108°F or greater.

2) Consider a dose of rFVIIa for ongoing coagulopathic bleeding.

3) Administer THAM (non-bicarbonate buffer) to maintain pH > 7.2.

4) Administer Ca++ after every four units of pRBCs and/or to keep ionized Ca++ > 1.0 (via i-STAT®).

7. ICU Resuscitation.

a. For patients who continue to have massive bleeding in the ICU the 1:1:1 approach in addition to all other DCR principles are still required. Additional doses of rFVIIa may also be indicated if acid/base and hematologic parameters are sufficient for its effectiveness (pH> 7.1, PLT> 50,000, FGN > 100).

8. Conclusion

a. The approach to a critically injured soldier, marine, sailor, or airmen requires a significant expenditure of resources and the coordination of a diverse group of health care providers. This is frequently performed in the face of multiple casualties and limited resources. It is incumbent upon the lead trauma surgeon at each facility to be fully versed on available resources, and to employ them judiciously and appropriately.

b. Patients requiring massive transfusion should be resuscitated using damage control resuscitation principals as noted above.

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Approved by CENTCOM JTTS Director, JTS Director and Deputy Director and CENTCOM SG

APPENDIX A

Example of a Massive Transfusion Protocol

At a CENTCOM Level III Facility

Massive Transfusion (MT) Protocol: A flexible protocol for use in the Emergency Department (ED), Operating Room (OR) and Intensive Care Unit (ICU) which can be initiated or ceased by the site-specific provider as dictated by the patient's needs when in that specific venue. It consists of Batches as defined below, which vary in composition, but are directed toward approximating a 1:1:1:1 ratio of PRBC, FFP, platelets and cryoprecipitate (cryo).

- **Pack One:** 4u PRBC and 4u FFP, should consider 6pk Platelets, cryo and +/- Factor VII (obtained from Pharmacy) at this time if patient received 4uPRBC/4uFFP Emergency release blood.
- **Pack Two:** 4u PRBC and 4u FFP
- **Pack Three:** 4u PRBC, 4u FFP, 6pk Platelets, cryo and +/- Factor VII (obtained from Pharmacy)
- Pack Five: 4u PRBC, 4u FFP, 6pk platelets, and cryo
- A reassessment of the progress of the resuscitation, hemostasis and the need to continue the MT Protocol should be conducted between the providers taking care of the patient at that time
- **Packs Six and Seven** are identical to packs Four and Five
- **Packs Eight and Nine** are identical to packs Four and Five

Definitions

Emergency Release:	Uncrossmatched 4u PRBC (2u O+ and 2u O-) and 4u AB FFP
Pack:	A single group of type-specific, crossmatched 4u PRBC and 4u FFP, which later in the Protocol, may include cryo, Platelets and/or Factor VII

Flow/order of resuscitation using MT Protocol

1. Patient arrives in ED. Initial survey, securing of airway and resuscitation are initiated by ED provider. Trauma Team begins consideration of blood transfusion needs.
2. Surgeon who will be taking the patient to the OR decides:
   - Blood is not needed at the present time.
   - Only use "Emergency Release" of uncrossmatched 4u PRBC and 4u FFP.
   - Initiate MT Protocol: 4u PRBC and 4u FFP immediately, Blood Bank begins creating Batch One (Emergency Release can be used to start, but is not counted as Pack One).
3. In the OR, the anesthesia provider, in ongoing evaluation of hemodynamics, lab studies and hemostatic control as per the operating surgeon, decides to continue the MT Protocol, initiate it if not already done so in the ED or terminate it and notify the Blood Bank of that decision if the patient has remained stable.
4. Once in the ICU, the critical care provider now has responsibility for initiating, continuing or terminating the MT Protocol (and notifying the Blood Bank as appropriate) as the patient's condition and lab studies dictate.

APPENDIX B

Last-in, First Out Policy

Goal: In patients requiring massive transfusion (MT), a concerted effort is made to give patients younger units of PRBCs (i.e. preferably less than 14 days old, but the youngest available nonetheless).

The rationale for this policy is as follows:

1. Multiple retrospective analyses of various patient groups have suggested increased complications of transfusion with "older" units of PRBCs, presumably due to the development of a "storage lesion": which includes increased proinflammatory factors, acidosis, increased free hemoglobin, and decreased RBC deformability.
2. The people most likely to suffer the consequences of complications of "older" units of blood are those requiring a higher dose (e.g. multiple transfusions)
3. Therefore an effort is being made in theater to utilize "younger" (Last in, first out) blood for MT patients and those suspected of needing MT upon presentation to the MTF.

For all MT patients, the policy of “Last in First Out” (LIFO) will be applied for all blood products provided to the surgical/ICU team. The CENTCOM Command Surgeon’s staff, in conjunction with CENTCOM J4, the Armed Services Blood Program (ASBP) and in-theater personnel, have developed an extensive logistical process that helps ensure that certain Level III facilities in the CENTCOM AOR are adequately supported with the newest and freshest pRBCs, with current time from donation to availability in theater as low as 4 days.

APPENDIX C

RECOMBINANT FACTOR VIIa

1. Background. The most critically injured casualties often present hypothermic (T < 96°F), acidemic (base deficit < 6), and coagulopathic (INR > 1.5). All three conditions contribute to worsening bleeding. Interventions aimed at reversing coagulopathy, starting as soon after arrival as possible, may improve casualty survival.[1]

In a recent prospective, randomized human trauma study[2], rFVIIa was shown to be effective in decreasing transfusion requirements, including those patients requiring massive transfusion (pRBCs ≥ 10 units/24 hours), in humans with life-threatening hemorrhage, including patients with hypothermia (30-33 degrees C; Ph > 7.1). However, rFVIIa is 90% inactivated in patients with profound acidosis (Ph < 7.1), based on in-vitro data. Although this study was not powered to show safety, with 301 patients randomized, trends in favor of positive outcomes, adverse events, mortality, ventilator-free days, and ICU-free days were observed.

In a recently published retrospective review[3] of records for trauma admissions to Combat Support Hospitals in Iraq between Jan 04 and Oct 05, a total of 117 patients requiring a massive transfusion and receiving rFVIIa were identified. Complete records were available for review in 61 patients. Of those, 17 received rFVIIa early, or before 8 units of pRBCs had been transfused, while 44 received the drug late, or after 8 units pRBCs were given. At admission, temperature, Glasgow Coma Scale score, base deficit, hemoglobin, platelets, prothrombin time/International Normalized Ratio, and Injury Severity Score were similar in both groups, as were the number of administered units of fresh frozen plasma, fresh whole blood, cryoprecipitate, and crystalloid. Although no statistically significant survival benefit was seen, this review demonstrated that early administration of rFVIIa decreased red blood cell use by 20% (5 units) in trauma patients requiring massive transfusion. It is well documented that increased exposure to blood products increases the risk of infection, multi-organ failure, and mortality. In addition, the FDA has acknowledged that decreased blood transfusion is an appropriate end-point when considering the evaluation of resuscitation interventions.

In an another article[6], a retrospective review of combat casualty patients with severe trauma (ISS > 15) and massive transfusion (pRBCs ≥ 10 units/24 hours) admitted to one Combat Support Hospital in Baghdad, Iraq, was conducted. Admission vital signs and laboratory data, blood products, Injury Severity Score (ISS), 24-hour and 30-day mortality, and severe thrombotic events were compared between patients who received rFVIIa and those who did not receive rFVIIa. Of 124 patients who received massive transfusion, 49 patients received rFVIIa and 75 patients did not. ISS scores and vital signs did not differ between the two groups. A statistically significant decrease in mortality was demonstrated in the group who received rFVIIa at 12 hours, 24 hours, and 30 days. When rFVIIa was given at a median of 2 hours from admission, an association with decreased mortality was seen. There was no statistical difference in the incidence of severe thrombotic events (DVT, PE, stroke) between the study groups.

2. FDA Position.

a. FDA Approved Use: Recombinant Factor VIIa is FDA-approved for use during critical bleeding or surgery in hemophiliac patients with inhibitors to Factor VIII or IX.

b. Unlabeled Use: Recombinant Factor VIIa is not FDA-approved to stop uncontrolled hemorrhage in severe trauma patients, but has been studied in randomized trials and is in use in civilian trauma centers. It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.

c. Potential adverse events:[7] In November 2005 (following publication of the data in Reference 2 the FDA issued new "Warnings and Adverse Reactions" to the labeling for Novoseven® Coagulation Factor VIIa (Recombinant). This new information is based on data from post-marketing studies and routine safety surveillance. The additional adverse events that were added are based on clinical studies of off-label uses (non-hemophilia patients) and on post-marketing safety surveillance. The following additional adverse events were reported in both labeled and unlabeled indications: high D-dimer levels and consumptive coagulopathy; thromboembolic events including myocardial infarction, myocardial ischemia, cerebral infarction, and/or ischemia; thrombophlebitis, arterial thrombosis, deep vein thrombosis and related pulmonary embolism, and isolated cases of hypersensitivity.

3. Mechanism. Recombinant Factor VIIa is activated in combination with tissue factor at sites of endothelial injury. High doses of rFVIIa result in the accelerated generation of thrombin. The resulting clots are stronger and more resistant to fibrinolysis than normal clots.[8] The potential effectiveness of rFVIIa degrades with time in the patient with poorly controlled hemorrhage due to fibrinogen, platelet and coagulation factor consumption, and dilution. These patients may require clotting factors and platelet supplementation prior to administration of rFVIIa. In the forward surgical setting this supplementation is available by the early administration of fresh whole blood followed by rFVIIa.

4. Considerations for Use.

The extent of the risk of thrombotic adverse events after treatment with rFVIIa is not known, but is considered to be low. Coagulapathy is a major contributing factor to bleeding-related mortality, particularly when associated with metabolic acidosis and hypothermia. Additional factors contributing to coagulopathy in trauma patients are hemodilution and platelet dysfunction resulting from massive blood transfusion or fluid resuscitation. Patients who receive rFVIIa should be monitored for signs or symptoms of thrombosis.

Faced with the increase rate of massive transfusion inherent after military wounding, military clinicians have developed aggressive guidelines to pre-empt or reverse coagulopathy in patients requiring massive transfusions in the Level IIb/III facilities. These guidelines fall under the term "Damage Control Resuscitation" and include the use of thawed plasma (1:1 ratio with pRBCs), apheresis platelets, pooled cryoprecipitate, fresh whole blood, and rFVIIa. Recombinant activated factor VII was originally developed for the treatment of patients with hemophilia who developed inhibitors to Factor VIII or Factor IX. However, rFVIIa is used in virtually all Level I trauma centers in the US, usually as part of a massive transfusion protocol. Although rFVIIa has been associated with pathologic thrombosis, in the only prospective, randomized study of injured patients receiving rFVIIa compiled to date, the clinical VTE rate was no different between patients who received rFVIIa and those that did not (2% vs. 3% in blunt trauma; 4% vs. 3% in penetrating trauma).[2] At a recent DOD review, a group of Senior Civilian Surgeons reviewed data on 615 severely injured combat casualties from 2004-2006 compiled from the Joint Theater

Trauma Registry. The DVT rate was 7.5%, with a PE incidence of 3.8% and there was no apparent difference in VTE between groups that received rFVIIa and those who did not. Among the most severely injured combat casualties who required a massive transfusion, the thrombotic rate in patients who did not receive rFVIIa was 13% vs. 18% for those who did (not significantly different). Conversely, rFVIIa significantly improved survival in a subgroup of severely injured and massively transfused casualties ($p < 0.05$).[6]

5. Guidelines for administration in the deployed surgical setting.

The use of this product should be reserved for those patients likely to require massive transfusion (e.g. significant injury and 3 or 4 risk factors of Massive Transfusion) and is at the discretion of the treating physician. It should be the judgement of the provider that the casualty has a life-threatening hemorrhagic injury and high potential for development of coagulopathy or presence of coagulopathy.

6. Protocol for Use

a. Infuse rFVIIa at dose of 90-120 mcg/kg IV push.

b. If coagulopathic bleeding continues 20 minutes after infusion:

1) Administer 2 additional units fresh whole blood or 4 U FFP and/or 6 pack platelets

2) Redose rFVIIa 90-120 mcg/kg IV push and repeat ii)[1]

7. Administration Limits

a. 3 doses within a 6 hour period

b. If bleeding persists after 3 doses, attention should be directed toward conservation of resources. Consult senior surgeon at the MTF before administering additional rFVIIa.

8. Storage

a. Refrigeration at 4^{o} C. (range 2-8^{o} C.).

b. Reconstitution is with sterile water for injection at room temperature.

c. The reconstituted solution may be used up to 24 hours after reconstitution.

d. **The FDA has recently approved a non-heat sensitive rFVIIa. This product will be distributed throughout the AOR to replace expended stocks.**

9. Relative Contraindications.[7] Known hypersensitivity to rFVIIa or any of its components. Known hypersensitivity to mouse, hamster, or bovine proteins.

10. Absolute Contraindications. Active cardiac disease.

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